Pain relief in metastatic cancer other than breast and prostate gland following transsphenoidal hypophysectomy

A preliminary report

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Hypophysectomy was performed in six patients with advanced carcinoma other than from breast and prostate gland to alleviate pain. Two patients received significant and lasting relief of pain; one achieved relief but died from progression of disease 5 weeks after surgery; one patient, initially relieved, had recurrence of pain 3 months later; one had about 50% relief; and one received no benefit. Possible mechanisms for pain relief include changes in pituitary hormones, prostaglandins, and the newly isolated brain peptides, alpha and beta endorphin. These preliminary observations will require further critical evaluation in a larger series to determine the effectiveness of hypophysectomy in relieving pain in cancer other than from the breast and prostate. The results, nevertheless, do imply that a different approach to pain, namely endocrine manipulation, may be beneficial in certain cancer patients.

KEY WORDS • hypophysectomy • pain relief • metastatic cancer • pituitary hormones
TABLE 1

Effect of hypophysectomy on pain in cancer patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, Sex</th>
<th>Primary Site</th>
<th>Location of Pain</th>
<th>Pain Relief</th>
<th>Analgesic Requirements Preoperative</th>
<th>Postoperative</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21, M</td>
<td>testicle</td>
<td>lumbar spine, hip</td>
<td>relieved</td>
<td>Demerol, 75 mg, Phenergan, 25 mg, every 3-4 hrs</td>
<td>one Percodan daily for 2 weeks only</td>
<td>alive, pain-free 12 months postop</td>
</tr>
<tr>
<td>2</td>
<td>60, F</td>
<td>adrenal gland</td>
<td>abdomen hip, pelvis</td>
<td>relieved</td>
<td>codeine, 60 mg × 3 daily (not effective)</td>
<td>none</td>
<td>remained pain-free until death 8 mos postop</td>
</tr>
<tr>
<td>3</td>
<td>46, M</td>
<td>pancreas</td>
<td>midthoracic spine, abdomen</td>
<td>relieved</td>
<td>methadone, 7 mg, Percodan, × 4-5 daily</td>
<td>Percodan, 1-2 daily</td>
<td>remained pain-free until death 2 mos postop</td>
</tr>
<tr>
<td>4</td>
<td>43, M</td>
<td>urethra</td>
<td>abdomen, pelvis</td>
<td>relieved</td>
<td>methadone, 20 mg every 4 hrs</td>
<td>Percodan, 1 every 4 to 6 hrs, 3 mos postop started methadone</td>
<td>pain recurred to original intensity 3 mos postop; died 6 mos postop</td>
</tr>
<tr>
<td>5</td>
<td>60, M</td>
<td>pancreas</td>
<td>abdomen, left testicle, lumbar spine</td>
<td>about 50% relief</td>
<td>Demerol, 50-75 mg &amp;/or morphine, 10 mg, &amp;/or methadone, 16 mg every 4-6 hrs</td>
<td>codeine, 30-60 mg or Tylenol or Talwin × 2 daily</td>
<td>died 3 mos postop</td>
</tr>
<tr>
<td>6</td>
<td>43, M</td>
<td>testicle</td>
<td>lumbar spine, flank</td>
<td>no relief</td>
<td>methadone, 10 mg every 4 hrs</td>
<td>codeine, 30-60 mg every 4 hrs, later methadone 10 mg every 4 hrs</td>
<td>died 4 mos postop</td>
</tr>
</tbody>
</table>

with adenocarcinoma of the urethra, one with seminoma, and one with embryonal carcinoma of the testis) underwent transsphenoidal hypophysectomy. The results form the basis of this preliminary report.

**Case Material and Methods**

All six patients had pathological verification of their disease, and in all cases dissemination of the cancer had occurred. Endocrine studies were performed immediately before and 10 days after hypophysectomy. The studies included radioimmunoassay determination of luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, testosterone, total thyroxine (T4), free T4, thyroid stimulating hormone (TSH), growth hormone, and prolactin (both fasting and 1, 2, 3, and 4 hours following chlorpromazine stimulation). Hypophysectomy was performed by the transsphenoidal microsurgical technique described by Hardy, with the patient under general anesthesia.

All operations were performed by the same surgeon (G.T.T.) and in each instance, it was believed that a complete pituitary ablation was accomplished. Informed consent was obtained from each patient. A thorough and frank discussion was held with each patient and his family before hypophysectomy, and all were fully aware that there was no background of experience for treating pain by hypophysectomy in their particular cancer. The postoperative endocrine management of patients undergoing transsphenoidal hypophysectomy has been described elsewhere.8,10

**Results**

Following hypophysectomy (Table 1), two patients received significant and lasting relief of pain; one achieved relief but died from progression of disease 2 months after surgery; one patient, initially relieved, had recurrence of pain 3 months later; one received about 50% relief; and one enjoyed no benefit. Relief usually occurred within 24 hours of the
operative procedure. With one possible exception, none of the patients showed objective evidence of remission of disease (that is, arrest or regressive change in the tumor) as a result of hypophysectomy. The one possible exception (Case 1) demonstrated slight shrinkage of a retroperitoneal mass as measured by serial intravenous pyelograms. In each case there was a significant reduction following hypophysectomy in the patient's need for analgesic medication. In some instances, postoperative analgesics were taken for the mild pain and discomfort related to the transsphenoidal operation.

All patients tolerated surgery well. Four patients developed partial diabetes insipidus following surgery. This complication was not considered disabling, and in each case was controlled by the oral administration of 500 mg clofibrate (Atromid-S) four times daily. Two of the four patients subsequently were able to discontinue clofibrate without recurrence of the diabetes insipidus. There were no other complications of surgery. The results of endocrinological studies performed 10 days after hypophysectomy were consistent with complete hypophysectomy.

The following case illustrates pain relief achieved by one patient following transsphenoidal hypophysectomy:

Case 2. This 60-year-old woman was admitted to Emory University Hospital on March 23, 1976, for treatment of abdominal pain secondary to recurrence of an adrenal adenocarcinoma. She had developed rightsided abdominal pain in late 1973, and was evaluated at another hospital. In December, 1973, following diagnostic studies, she underwent resection of a well differentiated adenocarcinoma of the right adrenal cortex. The patient did well and was relatively free of pain until January, 1975, at which time she developed abdominal and right thigh pain. In May, 1975, she was found to have recurrence of tumor in the osseous pubis. Irradiation to the pelvis and chemotherapy resulted in partial relief of the thigh pain. In October, 1975, recurrent tumor was palpated in the abdomen. Her abdominal pain continued and was associated with intermittent nausea and vomiting. Despite chemotherapy with ortho-para-DDD the abdominal mass enlarged and her pain increased.

Examination revealed a slightly emaciated and chronically ill-appearing woman. There were two firm non-tender masses palpable in the right upper and lower quadrants of the abdomen. Except for a hematocrit of 32%, the routine laboratory studies were normal. X-ray films showed osteocytic lesions in the inferior ramus of the right pubis, ischium, and right acetabulum. Transfemoral arteriography revealed a large vascular tumor involving the superior aspect of the right kidney and the inferior aspect of the right lobe of the liver.

Endocrinological evaluation revealed that the tumor was a nonfunctioning adrenal tumor. On March 26, 1976, she underwent a transsphenoidal hypophysectomy. Except for developing partial diabetes insipidus, she had an uneventful postoperative course. She experienced complete relief of the abdominal and thigh pain within 24 hours of surgery and was discharged on the 11th postoperative day. After discharge, she was seen a total of four times in the clinic, the last time on August 31, 1976. The partial diabetes insipidus persisted and was controlled with clofibrate-S, 500 mg, four times daily. Significantly, the patient remained free of pain. She continued to lose weight and showed slow deterioration physically as a result of the recurrent tumor. She died on November 22, 1976.

Discussion

While a variety of possible mechanisms, including structural or regressive change in the tumor, placebo effect, nonspecific steroid effect, and removal of prolactin and/or growth hormone, may account for the pain relief following hypophysectomy, the most promising explanation may be related to endogenous opiate receptors and the newly discovered brain peptides with morphine-like properties. The discovery of highly specific opiate receptors in neuronal membranes 1,2 has created the notion that these receptors physiologically interact with a normally occurring opiate-like substance and thus initiated a search for these substances in mammalian brain extracts. Recently, Guillemin, et al., isolated a hexadecapeptide that they have termed "α-endorphin." 3 This substance, which was obtained from pituitary and hypothalamic tissue of the pig, inhibits electrically induced contractions of guinea pig ileum with a potency similar to morphine. Of perhaps greater significance is the recent isolation and identification of another substance with opiate-like properties termed \( \beta- \)
endorphin. This substance has been synthesized and has been shown to possess, on a molar basis, 18 to 33 times more potency than morphine. The mechanism of action and circumstances of potential release of endorphins either into brain substance, cerebrospinal fluid (CSF) and/or ventricular fluid, or peripheral circulation remain to be determined. However, it is interesting to speculate that the loss of shortloop feedback control due to pituitary ablation in humans is followed by release of factors such as α-and/or β-endorphin, which act in some as yet unknown manner to alleviate pain. Since the structure of both α- and β-endorphin is known, it will probably be possible ultimately to develop a radioimmunoassay for both endorphins thus allowing pre- and postoperative blood and/or CSF assays in hypophysectomized patients. It is possible that some insight into the potential role of the endorphins may be gained through this approach.

The results of this small clinical series raise the interesting possibility that certain instances of pain associated with metastatic cancer may be either mediated or significantly influenced by endocrine, as opposed to neural, mechanisms. Should this supposition prove true, it indicates that a new approach to the investigation of pain associated with cancer, namely, endocrine manipulation, may prove fruitful. For instance, it would be of considerable interest to determine the effects of known substances, such as somatostatin, levodopa, bromoergocryptine, and serotonin, that affect pituitary secretion on the pain of metastatic cancer, not only in patients with potentially endocrine-sensitive tumors such as breast and prostate gland cancer, but other malignancies as well.

References


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